



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/195, 31/22, 31/225 // C07C 323/59	A1	(11) International Publication Number: WO 91/18594 (43) International Publication Date: 12 December 1991 (12.12.91)
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(21) International Application Number: PCT/SE91/00388
(22) International Filing Date: 3 June 1991 (03.06.91)

(30) Priority data:
9002067-8 8 June 1990 (08.06.90) SE
9002275-7 28 June 1990 (28.06.90) SE

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(81) Designated States: AT, AT (European patent), AU, BB, BE
(European patent), BF (OAPI patent), BG, BJ (OAPI
patent), BR, CA, CF (OAPI patent), CG (OAPI patent),
CH, CH (European patent), CI (OAPI patent), CM
(OAPI patent), DE, DE (European patent), DK, DK
(European patent), ES, ES (European patent), FI, FR
(European patent), GA (OAPI patent), GB, GB (Euro-
pean patent), GN (OAPI patent), GR (European pa-
tent), HU, IT (European patent), JP, KP, KR, LK, LU,
LU (European patent), MC, MG, ML (OAPI patent),
MR (OAPI patent), MW, NL, NL (European patent),
NO, PL, RO, SD, SE, SE (European patent), SN (OAPI
patent), SU, TD (OAPI patent), TG (OAPI patent), US.

Published

With international search report.

(54) Title: THE PHARMACOLOGICAL USE OF CERTAIN CYSTINE DERIVATIVES

(57) Abstract

A method for the treatment of diseases due to defects in the immune system using certain cystine derivatives and a phar-
maceutical preparation comprising these derivatives.

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THE PHARMACOLOGICAL USE OF CERTAIN CYSTINE DERIVATIVES5 Field of the Invention

The present invention relates to a new medical use of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N, N'-dicaprylylcystine, N,N'-
10 diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester and N,N'-diisovalerylcystine dimethyl ester in racemic forms or in the form of optical D or L isomers.

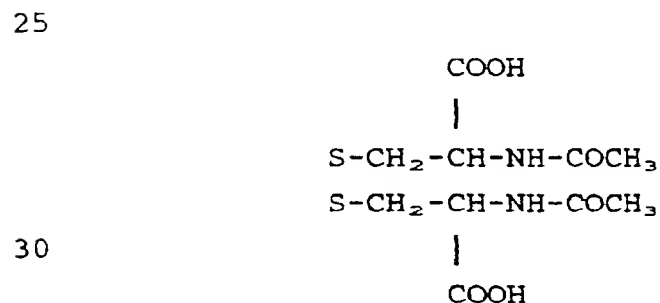
In particular the invention relates to the use of the
15 abovementioned compounds for the preparation of medicaments with immunomodulating action, particularly immunostimulating action.

Background of the Invention

20 N-Acetyl-L-cysteine is a compound widely used for treating chronic obstructive airway diseases/chronic bronchitis (for further references see Multicentre Study Group. Long-term oral acetylcysteine in chronic bronchitis. A
25 double-blind controlled study. Eur. J. Respir. Dis. 1980, 61 (suppl. 111), 93-108; Boman, G., Bäcker, U., Larsson, S., Melander, B., and Wählander, L. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis. Report of a trial organized by the Swedish Society for Pulmonary
30 Disease. Eur. J. Respir. Dis. 1983, 64, 405-415; and British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airway obstruction. Thorax 1985, 40, 832-835). The mechanism of action of the
35 compound is not disclosed; its effect has been attributed to mucolytic properties (see Multicentre Study Group.

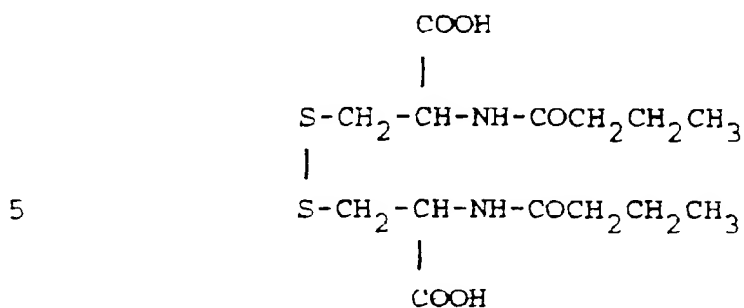
Long-term oral acetylcysteine in chronic bronchitis. A double-blind controlled study. Eur. J. Respir. Dis. 1980, 61 (suppl. 111), 93-108; Boman, G., Bäcker, U., Larsson, S., Melander, B., and Wåhlander, L. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis. Report of a trial organized by the Swedish Society for Pulmonary Disease. Eur. J. Respir. Dis. 1983, 64, 405-415; and British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airway obstruction. Thorax 1985, 40, 832-835), antioxidant properties (see Aruoma, O.I., Halliwell, B., Hoey, B.M., and Butler, J. Free Radical Biol. Med. 1989, 6, 593-597), and also immunomodulating properties (see Bergstrand, H., Björnson, A., Eklund, A., Hernbrand, R., Eklund, A., Larsson, K., Linden M., and Nilsson, A. Stimuli-induced superoxide radical generation in vitro by human alveolar macrophages from smokers: Modulation by N-Acetylcysteine treatment in vivo. J. Free Radicals Biol. & Med. 2, 1986, 119-127).

The present invention deals with the disulfide of N-acetylcysteine, that is N,N'-diacetylcystine (in the following referred to as DiNAC), i.e. the compound of the formula:

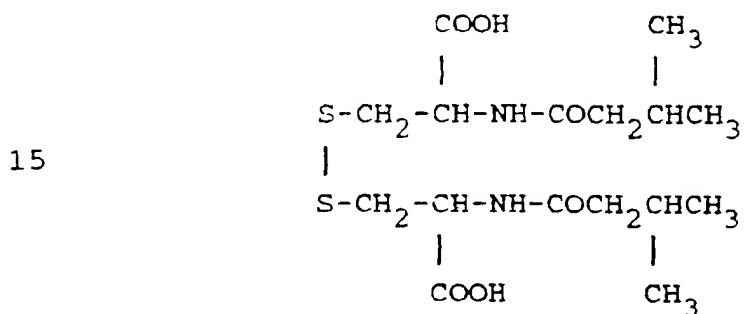


N,N' - dibutyrylcystine (in the following referred to as diBUT), i.e. the compound of the formula:

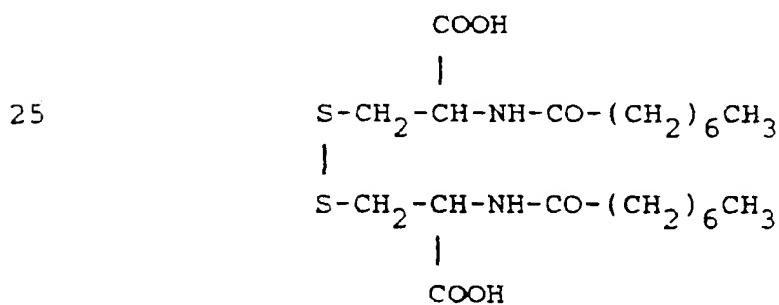
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N,N'-diisovalerylcystine (in the following referred to as
 10 diVAL), i.e. the compound of the formula

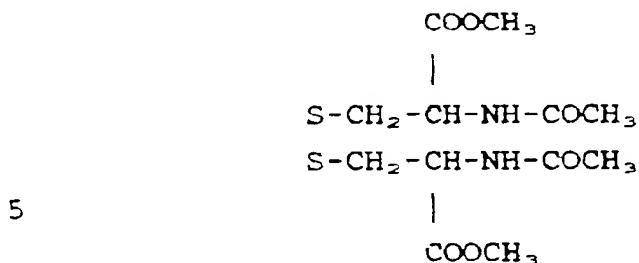


20 N,N'-dicaprylylcystine (in the following referred to as
 diCAP), i.e. the compound of the formula

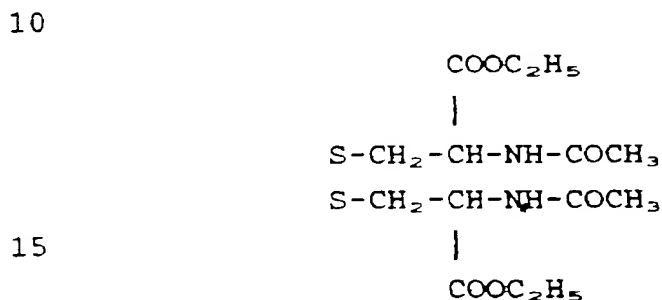


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N,N'-diacetylcystine dimethyl ester (in the following
 referred to as diMeNAC), i.e. the compound of the formula:

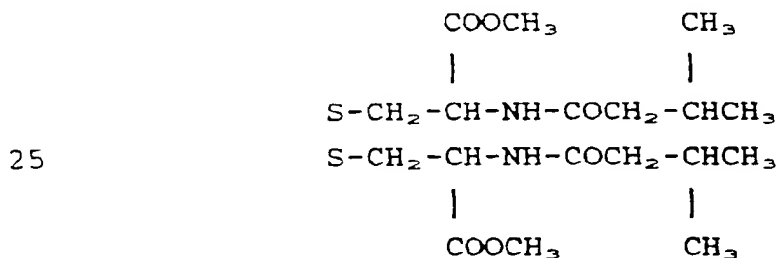


N,N'-diacetylcystine diethyl ester (in the following referred to as diEtNAC), i.e. the compound of the formula:



and N,N'-diisovalerylcystine dimethyl ester (in the following referred to as diMeVAL), i.e. the compound of the formula:

20



The invention deals with the above mentioned compounds in racemic form as well as the isomeric D and L forms of the compounds. Of particular interest are the compounds having the L configuration, particularly interesting is N,N'-diacetyl-L-cystine.

35 The invention also deals with the compounds in the form of their physiologically acceptable salts such as the salts

of sodium, potassium, ammonium, calcium or magnesium. Also included are salts of the compounds diNAC, diBUT, diVAL and diCAP with pharmaceutically acceptable organic bases.

5

The above mentioned compounds have previously been described in the patent literature as well as in the scientific literature. DiNAC in the following publications: US 4827016; EP 300100; US 4724239; US
10 4708965; DE 2326444; Wilson, I.D., and Nicholson, J.K. Analysis of thiols and disulfides in Sulphur-containing drugs and related organic compounds. Chemistry, Biochemistry and Toxicology (ed L.A. Damani) Vol. 2A. Analytical, biochemical and toxicological aspects of
15 sulphur xenobiochemistry. Ellis Horwood Series in Biochemical Pharmacology (Halsted Press: a division of John Wiley & Sons) Chichester 1989, p. 45; and Sjödin K., Nilsson E., Hallberg, A., and Tunek, A. Metabolism of N-Acetyl-L-cysteine. Some structural requirements for the
20 deacetylation and consequences for the oral bioavailability. Biochem. Pharmacol. 1989, 38, 3981-3985). In US 4827016 the compound is claimed to be effective for topical treatment of dermal inflammations which are induced and propagated by leukotrienes.

25

The remaining compounds have also been described in the literature. (See for instance, for diMeNAC: Bowman, W.R. Richardson, G.D. Tetrahedron Lett. 1981, 22, 1551-1554; for diEtNAC: Damico, R.A. Boggs, R.W. US 3952115 (1976);
30 for diVAL, diMeVAL: Martin, T.A. J. Med. Chem 1969, 12, 950-953), for diCAP: FR 8205 M, for diBUT: FR 2503151).

Nothing is reported or generally known concerning the pharmacological and/or therapeutic properties of these
35 compounds with respect to immunological systems or inflammatory diseases of the lung such as chronic

bronchitis.

Disclosure of the Invention

5 It has unexpectedly been found that the hereinbefore mentioned compounds diNAC, diBUT, diVAL, diCAP, diMeNAC, diEtNAC and diMeVAL in an experimental animal model for assessing a T-cell reactivity in vivo, i.e. the delayed type hypersensitivity (DTH) reaction in the mouse ear, are
10 highly potent and efficient immunostimulating agents, some being in the order of 100-1000 times more effective than the thiol NAC. Thus, in this model the compounds are highly effective immunostimulators with a potency and efficacy superior or equal to known immunostimulants such
15 as diethyl dithiocarbamate (DTC) or hydroxyethyl disulfide (HEDS; see St Georgiev, V. New synthetic immunomodulating agents. Trends in Pharmacological Science 1988, 446-451).

Therefore, the compounds DiNAC, diBUT, diVAL, diCAP,
20 diMeNAC, diEtNAC, diMeVAL and their D and L optical isomers may be used for treatment of diseases where a defect in the immune system and/or an ineffective host defence is at hand or can be suspected.

25 Examples of such diseases are chronic bronchitis and other inflammatory diseases of the airways such as asthma and rhinitis but also certain forms of autoimmune diseases like diabetes and rheumatoid arthritis and/or various malignant diseases. HIV infection or AIDS may be treated
30 with the compounds. Also atherosclerotic disease may be treated with the compounds.

Effective amounts of the compounds diNAC, diBUT, diVAL, diCAP, diMeNAC, diEtNAC, diMeVAL and their D and L optical
35 isomers for use in the treatment of the above mentioned

diseases are in the range 0.5-500 mg, preferably 5-50 mg, daily dose.

Synthesis of compounds

5

The compounds diNAC, diBUT, diVAL and diCAP may be prepared, for example, from L-cystine via acylation (see US 4827016; EP 300100; US 4724239; US 4708965; DE 2326444; Marshall, R., Winitz, M., Birnbaum, S.M. and Greenstein, J.P. J. Am. Chem. Soc. 1957, 79, 4538-4544; and Cecil, R. McPhee, J.B. Biochem. J. 1957, 66, 538-543) or through oxidative dimerization of the appropriate acylcysteines (see Snow, J.T., Finley, J.W. Friedman, M. Biochem. Biophys. Res. Commun. 1975, 64, 441-447).

15

The esters diMeNAC, diEtNAC and diMeVAL may be synthesized analogously, i.e. by acylation of the cystine methyl or ethyl esters as appropriate or by oxidative dimerisation of the respective N-acetyl cystine methyl or ethyl esters or N-isovalerylcysteine methyl ester. For examples of preparations, see Bonnett, R., Nicolaidow, P. J. Chem. Soc. Perkin Trans. I 1979, 1069-1077. Schaad, L.J., Werner, R.M., Dillon, L., Field, L., Tate, C.E. J. Med. Chem. 1975, 18, 344-351, and Martin, T.A. J. Med. Chem. 1969, 12, 950-953.

Effects of compounds in a model of delayed type hypersensitivity in the mouse

30 The property of the compounds diNAC, diBUT, diVAL, diCAP, diMeNAC, diEtNAC and diMeVAL to stimulate immune responses is illustrated by their efficacy in a model of the delayed type hypersensitivity (DTH) reaction in the mouse.

35 Both male and female Balb/c mice obtained from Bomholtsgaard (Denmark) and Charlie Rivers (England), were

used at the weight of 18-20 gram. 4-ethoxymethylene-2-phenyloxazolone (OXA) was purchased from BDH (England) and served as an antigen in this test.

5 The mice were sensitized, Day 0, by epicutaneous application of 150 μ l absolute ethanol-acetone (3:1) solution containing 3% OXA on the shaved thorax and abdomen. Treatment with the L-form of diNAC, diMeNAC, diEtNAC, diMeVAL, or vehicle (phosphate buffer, pH 7.0)
10 was initiated by oral feeding immediately after sensitization and continued once daily to Day 6. Seven days (Day 6) after the sensitization both ears of all mice were challenged on both sides by topical application of 20 μ l 1% OXA dissolved in peanut oil. Ear thickness was
15 measured prior to and 24 or 48 hours after challenge using an Oditest spring calliper. Challenges and measurements were performed under light pentobarbital anesthesia. The intensity of the DTH reactions was expressed according to the formula: $T_{t24/48} - T_{t0}$ μ m units, where t_0 , t_{24} and t_{48}
20 represent the ear thickness before and 24 or 48 hours after challenge, respectively, in an individual test (T). The results were expressed as the mean \pm S.E.M. The level of significance between means of the groups was obtained by Student's two-tailed t-test. Tables 1 and 2 show the
25 results from 24 and 48 hours measurements, respectively, from a representative experiment with the L-form of diNAC. The results show that L-diNAC, after oral administration, caused a significant increase of the ear thickness in a concentration-response manner.

Table 1

Ear thickness 24 hours after challenge of animals treated with the indicated doses of L-diNAC or vehicle.

5

	Conc. $\mu\text{mol/kg}$	N	Diff. $T_{t24}-T_{t0}$	S.E.M.	Sign.
10	Buffer	13	7.85	0.32	
	NaCl	10	7.90	0.30	n.s.
	0.03	10	13.75	0.47	***
	0.30	10	15.70	0.48	***
15	3.0	10	18.30	1.02	***
	30.0	15	20.67	0.67	***

***: $p < 0.001$

20

Table 2

5

Ear thickness 48 hours after challenge of animals treated with the indicated doses of L-diNAC or vehicle.

10	Conc. μmol/kg	N	Diff $T_{t48} - T_{t0}$	S.E.M.	Sign.
<hr/>					
	Buffer	14	9.64	0.35	
15	NaCl	10	9.85	0.54	n.s.
	0.03	10	11.65	0.27	***
	0.30	10	12.65	0.48	***
	3.0	10	14.95	0.55	***
	30.0	15	13.63	0.30	***
20	<hr/>				

***: $p < 0.001$

25 Table 3 gives the corresponding figures for ear thickness 24 and 48 hours after challenge of animals treated with diMeNAC and diEtNAC.

Table 3

5 Ear thickness 24 and 48 hours after challenge of animals treated with the L-forms of diMeNAC and diEtNAC.

10		Conc	N	Diff	S.E.M.	Sign.
		$\mu\text{mol/kg}$		$T_{t24}-T_{t0}$		
<hr/>						
		24 h				
15	Buffer		10	8.70	0.34	-
	diMeNAC	0.03	10	18.00	0.84	***
		3.0	10	12.55	0.88	**
20	diEtNAC	0.03	10	11.75	0.62	***
		3.0	10	13.05	0.59	***

25

(to continue...)

(...table 3)

		Conc μmol/kg	N	Diff T _{t48} -T _{t0}	S.E.M.	Sign.
		48 h				
10	diMeNAC	0.03	10	12.85	0.67	**
		3.0	10	13.35	0.67	***
	diEtNAC	0.03	10	13.15	0.53	***
		3.0	10	13.20	0.66	***
15						

** : $p < 0.01$

20 ***: $p < 0.001$

Pharmaceutical formulations

The described active substances can be included in
5 different dosage forms e.g. tablets, coated tablets,
gelatin capsules, solutions and aerosols.

For the preparation of tablets, coated tablets and gelatin
capsules the active substances can be combined with
10 pharmaceutically acceptable materials, e.g. lactose,
starch, dicalcium phosphate, microcrystalline cellulose,
polyvinylpyrrolidone, gelatin, cellulose derivatives,
colloidal silicone dioxide, talc and stearic acid or its
salts.

15

For the preparation of oral solutions suitable excipients
are water, saccharose, glucose, sorbitol, fructose and
xylitol.

20 The dosage forms can besides mentioned excipients contain
preservatives, stabilizers, viscosity regulating agents,
emulsifiers, sweetening agents, colouring agents,
flavouring agents, tonicity regulating agents, buffers or
antioxidants. They can also contain other therapeutically
25 valuable substances.

Example 1

Tablet containing 10 mg of active substance per tablet:

5	Active substance	10 mg
	Lactose	100 mg
	Potato starch	50 mg
	Polyvinylpyrrolidone	5 mg
10	Microcrystalline cellulose	15 mg
	Magnesium stearate	1 mg

Example 2

15 Direct compression tablet containing 5 mg of active substance per tablet:

	Active substance	5 mg
	Lactose, anhydrous	150 mg
20	Microcrystalline cellulose	50 mg
	Colloidal silicon dioxide	1 mg
	Magnesium stearate	2 mg

25 If desired, the obtained tablets can be film coated with e.g. hydroxypropyl methylcellulose, hydroxypropyl cellulose or dimethylaminoethyl methacrylate methacrylic acid ester copolymer.

Example 3

30

Solution for injection containing active substance 1 mg/ml

	Active substance	1.0 mg
	Sodium chloride	8.8 mg
35	Water for injection	to 1 ml

Example 4

Oral solution containing active substance 1 mg/ml

5	Active substance	1.0 mg
	Sorbitol	150 mg
	Glycerin	100 mg
	Disodium edetate	0.5 mg
	Preservative	q.s.
10	Flavour	q.s.
	Water, purified	to 1 ml

Example 5

15 Powder aerosol giving 1 mg per dose

The micronized active substance can be filled into a powder inhaler device e.g. Turbuhaler^R giving 1 mg/dose.

CLAIMS

1. The use of racemic N,N'-diacetylcystine, N,N'-
dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-
5 dicaprylylcystine, N,N'-diacetylcystine dimethyl
ester, N,N'-diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
thereof for the preparation of medicaments with
10 immunomodulating action.
2. The use of the L optical isomers of N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
15 diacetylcystine dimethyl ester, N,N'-diacetylcystine
diethyl ester, N,N'-diisovalerylcystine dimethyl
ester, or a physiologically acceptable salt thereof
for the preparation of medicaments with
immunomodulating action.
- 20 3. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
25 diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
thereof for the preparation of medicaments with
effect against chronic bronchitis.
- 30 4. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-diacetylcystine
35 diethyl ester, N,N'-diisovalerylcystine dimethyl
ester, or a physiologically acceptable salt thereof

for the preparation of medicaments with effect against chronic bronchitis.

5. The use according to claim 1 of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with effect against asthma.
6. The use according to claim 2 of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, or a physiologically acceptable salt thereof for the preparation of medicaments with effect against asthma.
7. The use according to claim 1 of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with effect against rhinitis.
8. The use according to claim 2 of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-

- 5 diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
preparation of medicaments with effect against
rhinitis.
9. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
10 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
15 thereof for the preparation of medicaments with
effect against diabetes.
10. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
20 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
25 preparation of medicaments with effect against
diabetes.
11. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
30 diisovalerylcystine, N,N'-dicaprylylcystine,
N,N'-diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L
optical isomers thereof or a physiologically
35 acceptable salt thereof for the preparation of
medicaments with effect against rheumatoid

arthritis.

12. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
5 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
10 preparation of medicaments with effect against
rheumatoid arthritis.
13. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
15 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
20 thereof for the preparation of medicaments with
effect against malignant diseases.
14. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
25 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
30 preparation of medicaments with effect against
malignant diseases.
15. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
35 diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-

5 diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
thereof for the preparation of medicaments with
effect against HIV infections/AIDS.

10 16. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
preparation of medicaments with effect against HIV
15 infections/AIDS.

20 17. The use according to claim 1 of racemic N,N'-
diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, D and L optical
isomers thereof or a physiologically acceptable salt
thereof for the preparation of medicaments with
25 effect against atherosclerotic disease.

30 18. The use according to claim 2 of the L optical isomers
of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-
diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-
diacetylcystine dimethyl ester, N,N'-
diacetylcystine diethyl ester, N,N'-
diisovalerylcystine dimethyl ester, or a
physiologically acceptable salt thereof for the
preparation of medicaments with effect against
35 atherosclerotic disease.

19. The use according to claim 2 of N,N'-diacetyl-L-cystine.
20. A pharmaceutical preparation for use in the treatment of diseases where an immunomodulating substance is effective comprising as active ingredient a compound as defined in claim 1.
21. A pharmaceutical preparation according to claim 20 in dosage unit form.
22. A pharmaceutical preparation according to claims 20-21 comprising the active ingredient in association with a pharmaceutically acceptable carrier.
23. A pharmaceutical preparation according to claims 20-22 comprising as active ingredient N,N'-diacetyl-L-cystine.
24. A method for the treatment of diseases due to defects in the immune system, particularly chronic bronchitis, asthma, rhinitis, diabetes, rheumatoid arthritis, malignant diseases, HIV infection/AIDS and atherosclerotic disease, in mammals including man, characterized by the administration to a host in need of such treatment of an effective amount of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethylester, N,N'-diacetylcystine diethylester, N,N'-diisovalerylcystin dimethyl ester, D and L optical isomers thereof or a

physiologically acceptable salt thereof, optionally together with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00388

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: A 61 K 31/195, 31/22, 31/225//C 07 C 323/59																							
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 30%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="height: 40px; vertical-align: top; padding: 5px;">IPC5</td> <td style="vertical-align: top; padding: 5px;">A 61 K; C 07 C</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸</div> <p style="padding: 5px;">SE,DK,FI,NO classes as above</p>			Classification System	Classification Symbols	IPC5	A 61 K; C 07 C																	
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IPC5	A 61 K; C 07 C																						
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category *</th> <th style="width: 70%; padding: 5px;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 20%; padding: 5px;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">EP, A1, 0300100 (MORGAN LEE ROY) 25 January 1989, see claims 1, 12, 19-24, 25, 32, 39-42; p. 4, l. 14-19</td> <td style="vertical-align: top; padding: 5px;">1-19</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">X</td> <td style="text-align: center; padding: 5px;">--</td> <td style="vertical-align: top; padding: 5px;">20-23</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">US, A, 4827016 (L. R. MORGAN) 2 May 1989, see col. 5, l. 49-67; col. 7, l. 25-45; col. 10, l. 34-61; col. 11, l. 55 - col. 12, l. 9; col. 12, l. 22-57</td> <td style="vertical-align: top; padding: 5px;">1-19</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">X</td> <td style="text-align: center; padding: 5px;">--</td> <td style="vertical-align: top; padding: 5px;">20-23</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">US, A, 4724239 (L.R. MORGAN) 9 February 1988, see claims 1-4, 6-10, 12, 13, 15; col. 2, l. 34-40</td> <td style="vertical-align: top; padding: 5px;">1-19</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">X</td> <td style="text-align: center; padding: 5px;">--</td> <td style="vertical-align: top; padding: 5px;">20-23</td> </tr> </tbody> </table>			Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	EP, A1, 0300100 (MORGAN LEE ROY) 25 January 1989, see claims 1, 12, 19-24, 25, 32, 39-42; p. 4, l. 14-19	1-19	X	--	20-23	A	US, A, 4827016 (L. R. MORGAN) 2 May 1989, see col. 5, l. 49-67; col. 7, l. 25-45; col. 10, l. 34-61; col. 11, l. 55 - col. 12, l. 9; col. 12, l. 22-57	1-19	X	--	20-23	A	US, A, 4724239 (L.R. MORGAN) 9 February 1988, see claims 1-4, 6-10, 12, 13, 15; col. 2, l. 34-40	1-19	X	--	20-23
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>																							
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search 28th August 1991 </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report 1991 -09- 11 </td> </tr> <tr> <td style="padding: 5px;"> International Searching Authority <div style="text-align: center; padding: 10px;"> SWEDISH PATENT OFFICE </div> </td> <td style="padding: 5px;"> Signature of Authorized Officer <div style="text-align: center; padding: 10px;"> Gerd Wranne </div> </td> </tr> </table>			Date of the Actual Completion of the International Search 28th August 1991	Date of Mailing of this International Search Report 1991 -09- 11	International Searching Authority <div style="text-align: center; padding: 10px;"> SWEDISH PATENT OFFICE </div>	Signature of Authorized Officer <div style="text-align: center; padding: 10px;"> Gerd Wranne </div>																	
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US, A, 4708965 (L.R. MORGAN) 24 November 1987, see claims 1-3, 5; col. 5, l. 50-67; col. 4, l. 19-28	1-19
X	--	20-23
A	Journal of Medicinal Chemistry, Vol. 18, No. 4, 1975 L.J. Schaad et al.: "Linear Regression Analysis of Inhibitory Potency of Organic Disulfides against Histoplasma capsulatum", see p. 347, compound no. 72	1-19
X	--	20-23
A	Journal of Medicinal Chemistry, Vol. 12, September 1969 T.A. Martin: "N-Acyl- and N-Sulfonylcysteine Derivatives", see page 950 - page 953 see p. 952, Table I, compounds no. 19 and 20; p. 950. right col., last paragraph - p. 951, left col. first paragraph	1-19
X	--	20-23
A	FR, M, 8205 (J.V. MORELLE ET AL.) 26 October 1970, see claims 1, 2; p. 2; first paragraph, l. 28-31	1-19
X	--	20-23
A	FR, A1, 2503151 (J.V. MORELLE ET AL.) 8 October 1982, see p. 3; claims	1-19
X	--	20-23
P,X	International Journal of Pharmaceutics, Vol. 62, 1990 A.H. Kahns et al.: "Prodrugs as drug delivery systems. 107. Synthesis and chemical and enzymatic hydrolysis kinetics of various mono- and diester prodrugs of N-acetylcysteine", see page 193 - page 205 see the whole article	1-23
X	Biochemical Pharmacology, Vol. 38, No. 22, 1989 K. Sjödin et al.: "Metabolism of N-acetyl-L-cysteine. Some structural requirements for the deacetylation and consequences for the oral bioavailability", see page 3981 - page 3985 see the whole article	1-23
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US, A, 3952115 (R.A. DAMICO ET AL.) 20 April 1976, see claims 1, 5, 6, 8-10; col. 5, l. 17-30; col. 9, l. 63 - col. 10, l. 5; col. 10, l. 68 - col. 11, l. 1 --	1-23
A	Tetrahedron Letters, Vol. 22, No. 16, 1981 W.R. Bowman et al.: "Reactions of thiolate anions with 2-substituted-2-nitropropanes", see page 1551 - page 1554 see p. 1552, the Table, last compound --	1-23
A	DE, A, 2326444 (THE PROCTER & GAMBLE CO.) 6 December 1973, see p. 7, 3:rd paragraph; p. 8; p. 20, 2:nd paragraph; p. 21, last paragraph; p. 22, last paragraph - p. 23, first paragraph --	1-23
A	Patent Abstracts of Japan, Vol 12, No 47, C475, abstract of JP 62-195356, publ 1987-08-28 SEIWA KASEI K.K. --	1-23
A	J. Org. Chem., Vol. 54, 1989 D.S. Kemp et al.: "Templates for Intramolecular O,N-Acyl Transfer via Cyclic Intermediates Derived from Mercury Derivatives of L-Cysteine: Progress toward a Mercury-Based Thiol Capture Strategy", see page 3853 - page 3858 see p. 3855, right col. 2:nd paragraph -- -----	1-23

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 24 it s/ because ~~they~~ relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods. [PCT Rule 39.1 (iv)].

2. ☐ Claim numbers..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00388**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 91-06-27. The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0300100	89-01-25	US-A- 4708965 US-A- 4827016	87-11-24 89-05-02
US-A- 4827016	89-05-02	US-A- 4724239 EP-A- 0300100 US-A- 4708965	88-02-09 89-01-25 87-11-24
US-A- 4724239	88-02-09	US-A- 4827016	89-05-02
US-A- 4708965	87-11-24	EP-A- 0300100 US-A- 4827016	89-01-25 89-05-02
FR-M- 8205	70-10-26	NONE	
FR-A1- 2503151	82-10-08	DE-A-C- 3212448 GB-A-B- 2097256 JP-B- 2042805 JP-A- 57183703 US-A- 4859653	82-11-11 82-11-03 90-09-26 82-11-12 89-08-22
US-A- 3952115	76-04-20	AT-B- 348847 AU-B- 506795 AU-D- 1235476 BE-A- 840351 CA-A- 1064316 CH-A- 623206 DE-A-B-C 2613786 FR-A-B- 2305938 GB-A- 1533780 JP-A- 51142551 NL-A- 7603445 SE-B-C- 423301 SE-A- 7603892	79-03-12 80-01-24 77-09-29 76-10-04 79-10-16 81-05-29 76-10-14 76-10-29 78-11-29 76-12-08 76-10-05 82-05-03 76-10-03
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DE-A- 2326444	73-12-06	JP-A- 49124244	74-11-28
		JP-B- 50037731	75-12-04
		NL-A- 7307293	73-11-27
		SE-B-C- 388113	76-09-27
		US-A- 3878305	75-04-15